Amendments to the Specification:

Please amend the specification to replace the original sequence listing as filed with the amended, substitute sequence listing, and computer readable form, concurrently submitted with this Amendment and Response. The sequence listing has been amended to add new sequence identifiers, SEQ ID NOS: 52-61, for the oligonucleotides presented in Figure 13 as filed.

Please delete the paragraph on page 19, lines 1-2 (paragraph 109 in the published application) and replace with the following paragraph:

--Figure 2 shows the DNA and protein sequence of the light chain variable (V_L) domain of mouse monoclonal antibody 5/44 (SEQ ID NO:7).--

Please delete the paragraph on page 19, lines 3-4 (paragraph 110 in the published application) and replace with the following paragraph:

--Figure 3 shows the complete sequence of the heavy chain variable domain (V_H) of mouse monoclonal antibody 5/44 (SEQ ID NO:8).--

Please delete the paragraph on page 19, lines 5-6 (paragraph 111 in the published application) and replace with the following paragraph:

--Figure 4 shows the strategy for removal of the glycosylation site and reactive lysine in CDR-H2 (SEQ ID NOS:9-12 and 14).--

Please delete the paragraph on page 19, lines 7-12 (paragraph 112 in the published application) and replace with the following paragraph:

--Figure 5 shows the graft design for the 5/44 light chain sequence (SEQ ID NO:7). DPK-9 is the human germ-line acceptor framework sequence (SEQ ID NO:17). Vertical lines indicate differences between mouse and human residues. Sequences underlined indicate donor residues that have been retained in the graft. CDRs are indicated in bold italicized letters (not shown for DPK-9). Graft gL1 has 6 donor framework residues (SEQ ID NO:19), gL2 has 7 (SEQ ID NO:20).--

Please delete the paragraph on page 19, lines 13-18 (paragraph 113 in the published application) and replace with the following paragraph:

--Figure 6 shows the graft design for the 5/44 heavy chain sequence (SEQ ID NO:8); DP7 is the human germ-line acceptor framework sequence (SEQ ID NO:21). Vertical lines indicate differences between mouse and human residues. Sequences underlined indicate donor residues that have been retained in the graft. CDRs are indicated ~~initalicized~~ in italicized, bold letters (not shown for DP7). Grafts gH4 (SEQ ID NO:24) and gH6 (SEQ ID NO:26) have 6 donor framework residues. Grafts gH5 (SEQ ID NO:25) and gH7 (SEQ ID NO:27) have 4 donor framework residues.--

Please delete the paragraph on page 19, line 22 (paragraph 117 in the published application) and replace with the following paragraph:

--Figure 10 shows the oligonucleotides for 5/44 gH1 and gL1 gene assemblies (SEQ ID NOS:32-47).--

Please delete the paragraph on page 19, line 25 (paragraph 120 in the published application) and replace with the following paragraph:

--Figure 13 shows the oligonucleotide cassettes used to make further grafts (SEQ ID NOS:52-61).--

Please delete the paragraph on page 19, lines 30-31 (paragraph 123 in the published application) and replace with the following paragraph:

--Figure 16 shows the full DNA and protein sequence of the grafted heavy and light chains (SEQ ID NO:31 and SEQ ID NO:30, respectively, for the heavy chain, and SEQ ID NO:29 and SEQ ID NO:28, respectively, for the light chain).--

Please delete the paragraph on page 22, line 20 - page 23, line 6 (paragraph 141 in the published application) and replace with the following paragraph:

--Examples of antibody carriers that may be used in the present invention include monoclonal antibodies, chimeric antibodies, humanized antibodies, human antibodies and biologically active fragments thereof. Preferably, such antibodies are directed against cell surface antigens expressed on target cells and/or tissues in proliferative disorders such as cancer. Examples of specific antibodies directed against cell surface antigens on target cells include without limitation, antibodies against CD22 antigen which is over-expressed on most B-cell lymphomas; G5/44, a humanized form of a murine anti-CD22 monoclonal antibody; antibodies against cell surface antigen CD33, which is prevalent on certain human myeloid tumors especially

acute myeloid leukemia; hP67.6, a humanized form of the anti-CD33 murine antibody (*see* U.S. Patent No. 5,773,001); an antibody against the PEM antigen found on many tumors of epithelial origin designated mP67.6 (*see* I.D. Bernstein et al., *J. Clin. Invest.* 79:1153 (1987) and I.D. Bernstein et al., *J. Immunol.* 128:867-881 (1992)); and a humanized antibody against the Lewis Y carbohydrate antigen overexpressed on many solid tumors designated hu3S193, (*see* U.S. Patent No 6,310,185 B1). In addition, there are several commercially available antibodies such as rituximab (Rituxan™) and trastuzumab (Herceptin™), which may also be used as carriers/targeting agents. Rituximab (Rituxan™) is a chimeric anti-CD20 antibody used to treat various ~~B-cell~~B-cell lymphomas and trastuzumab (Herceptin™) is a humanized anti-Her2 antibody used to treat breast cancer.--

Please delete the paragraph on page 48, lines 14-20 (paragraph 255 in the published application) and replace with the following paragraph:

--A potential N-linked glycosylation site sequence was observed in CDR-H2, having the amino acid sequence N-Y-T (Figure 3, SEQ ID NO:8). SDS-PAGE, Western blotting and carbohydrate staining of gels of 5/44 and its fragments (including Fab) indicated that this site was indeed glycosylated (not shown). In addition, a lysine residue was observed at an exposed position within CDR-H2, which had the potential to reduce the binding affinity of the antibody by providing an additional site for conjugation with an agent with which the antibody may be conjugated.--

Please delete the paragraph on page 48, line 21 - page 49, line 2 (paragraph 256 in the published application) and replace with the following paragraph:

--A PCR strategy was used to introduce amino acid substitutions into the CDR-H2 sequence in an attempt to remove the glycosylation site and/or the reactive lysine, as shown in Figure 4 (SEQ ID NOS:9-12 and 14). Forward primers encoding the mutations N55Q, T57A or T57V were used to remove the glycosylation site (Figure 4, SEQ ID NOS:10-12) and a fourth forward primer containing the substitution K60R, was generated to remove the reactive lysine residue (Figure 4, SEQ ID NO:14). A framework 4 reverse primer was used in each of these PCR amplifications. The PCR products were digested with the enzymes XbaI and ApaI and were inserted into pMRR14(544cH) (also cleaved with XbaI and ApaI) to generate expression plasmids encoding these mutants. The N55Q, T57A and T57V mutations ablate the glycosylation site by changing the amino acid sequence away from the consensus N-X-T/S while the K60R mutation replaces the potentially reactive lysine with the similarly positively

charged residue arginine. The resultant cH variant plasmids were co-transfected with the cL plasmid to generate expressed chimeric antibody variants.--

Please delete the paragraph on page 50, lines 15-20 (paragraph 263 in the published application) and replace with the following paragraph:

--Protein sequence alignment with consensus sequences from human sub-group I kappa light chain V region indicated 64% sequence identity. Consequently, for constructing the CDR-grafted light chain, the acceptor framework regions chosen corresponded to those of the human VK sub-group I germline O12,DPK9 sequence. The framework 4 acceptor sequence was derived from the human J-region germline sequence JK1 (SEQ ID NO:18).--

Please delete the paragraph on page 50, lines 21-29 (paragraph 264 in the published application) and replace with the following paragraph:

--A comparison of the amino acid sequences of the framework regions of murine 5/44 (SEQ ID NO:7) and the acceptor sequence (SEQ ID NO:17) is given in Figure 5 and shows that there are 27 differences between the donor and acceptor chains. At each position, an analysis was made of the potential of the murine residue to contribute to antigen binding, either directly or indirectly, through effects on packing or at the V_H/V_L interface. If a murine residue was considered important and sufficiently different from the human residue in terms of size, polarity or charge, then that murine residue was retained. Based on this analysis, two versions of the CDR-grafted light chain, having the sequences given in SEQ ID NO:19 and SEQ ID NO:20 (Figure 5), were constructed.--

Please delete the paragraph on page 50, line 31 - page 51, line 4 (paragraph 265 in the published application) and replace with the following paragraph:

--CDR-grafting of the 5/44 heavy chain was accomplished using the same strategy as described for the light chain. The V-domain of the 5/44 heavy chain was found to be homologous to human heavy chains belonging to sub-group I (70% sequence identity) and therefore the sequence of the human sub-group I germline framework VH1-3,DP7 was used as an acceptor framework. The framework 4 acceptor sequences were derived from human J-region germline sequence JH4 (SEQ ID NO:22).--

Please delete the paragraph on page 51, lines 5-10 (paragraph 266 in the published application) and replace with the following paragraph:

--A comparison of the 5/44 heavy chain with the framework regions is shown in Figure 6 where it can be seen that the 5/44 heavy chain (SEQ ID NO:8) differs from the acceptor sequence (SEQ ID NO:21) at 22 positions. Analysis of the contribution that any of these might make to antigen binding led to 5 versions of the CDR-grafted heavy chains being constructed, having the sequences given in SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26 and SEQ ID NO:27 (Figure 6).--

Please delete the paragraph on page 51, lines 13-30 (paragraph 267 in the published application) and replace with the following paragraph:

--Genes were designed to encode the grafted sequences gH1 and gL1, and a series of overlapping oligonucleotides were designed and constructed (Figure 10, SEQ ID NOS:32-47). A PCR assembly technique was employed to construct the CDR-grafted V-region genes. Reaction volumes of 100 µl were set up containing 10 mM Tris-HCl pH8.3, 1.5 mM MgCl2, 50 mM KCl, 0.001 % gelatin, 0.25 mM of dATP, dTTP, dCTP, and dGTP, 1 pmole each of the 'internal' primers (T1, T2, T3, B1, B2, B3), 10 pmole each of the 'external' primers (F1, R1), and 1 unit of Taq polymerase (AmpliTaq, Applied BioSystems, catalogue no. N808-0171). PCR cycle parameters were 94 °C for 1 minute, 55 °C for 1 minute and 72 °C for 1 minute, for 30 cycles. The reaction products were then run on a 1.5 % agarose gel, excised and recovered using QIAGEN spin columns (QIAquick gel extraction kit, cat no. 28706). The DNA was eluted in a volume of 30 µl. Aliquots (1 µl) of the gH1 and gL1 DNA were then cloned into the InVitrogen TOPO TA cloning vector pCR2.1 TOPO (catalogue no. K4500-01) according to the manufacturer's instructions. This non-expression vector served as a cloning intermediate to facilitate sequencing of a large number of clones. DNA sequencing using vector-specific primers was used to identify correct clones containing gH1 and gL1, creating plasmids pCR2.1 (544gH1) and pCR2.1(544gL1) (Figures 11 and 12).--

Please delete the paragraph on page 51, line 31 - page 52, line 13 (paragraph 268 in the published application) and replace with the following paragraph:

--An oligonucleotide cassette replacement method was used to create the humanized grafts gH4, 5, 6 and 7, and gL2. Figure 13 shows the design of the oligonucleotide cassettes (SEQ ID NOS:52-61). To construct each variant, the vector pCR2.1(544gH1) or pCR2.1(544gL1)) was cut with the restriction enzymes shown (XmaI/SacII for the heavy chain, XmaI/BstEII for the light chain). The large vector fragment was gel purified from agarose and was used in ligation with the oligonucleotide cassette. These cassettes are composed of 2

complementary oligonucleotides (shown in Figure 13, SEQ ID NOS:52-61), mixed at a concentration of 0.5 pmoles/µl in a volume of 200 µl 12.5 mM Tris-HCl pH 7.5, 2.5 mM $MgCl_2$, 25 mM NaCl, 0.25 mM dithioerythritol. Annealing was achieved by heating to 95 °C for 3 minutes in a water bath (volume 500 ml) then allowing the reaction to slow-cool to room temperature. The annealed oligonucleotide cassette was then diluted ten-fold in water before ligation into the appropriately cut vector. DNA sequencing was used to confirm the correct sequence, creating plasmids pCR2.1 (5/44-gH4-7) and pCR2.1 (5/44-gL2). The verified grafted sequences were then sub-cloned into the expression vectors pMRR14 (heavy chain) and pMR10.1 (light chain).--

Please delete the paragraph on page 52, lines 16-26 (paragraph 269 in the published application) and replace with the following paragraph:

--The vectors encoding grafted variants were co-transfected into CHO cells in a variety of combinations, together with the original chimeric antibody chains. Binding activity was compared in a competition assay, competing the binding of the original mouse 5/44 antibody for binding to Ramos cells (obtained from ATCC, a Burkitt's lymphoma lymphoblast human cell line expressing surface CD22). This assay was considered the best way to compare the grafts in their ability to bind to cell surface CD22. The results are shown in Figures 14 and 15. As can be seen, there is very little difference between any of the grafts, all performed more effectively than the chimeric at competing against the murine parent. The introduction of the 3 additional human residues at the end of CDR-~~H3~~H2 (~~gH5~~gH6 and gH7) did not appear to have affected binding.--